EXHIBIT M

March 1, 2016

Expert Report of Shelby F. Thames, Ph.D.

Prepared for

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF WEST VIRGINIA
CHARLESTON DIVISION

IN RE: ETHICON, INC., PELVIC REPAIR SYSTEM PRODUCTS LIABILITY LITIGATION	**Master File No. 2:12-MD-02327** **MDL 2327**
THIS DOCUMENT RELATES TO: *Wave 1 Cases*	**JOSEPH R. GOODWIN** **U.S. DISTRICT JUDGE**

I have been asked to analyze Ethicon's Prolene, the mesh material at issue in this medical device, and offer opinions concerning claims that the mesh used in Ethicon's product is not suitable for implantation. I have analyzed several other claims involving Ethicon's mesh devices used for the treatment of stress urinary incontinence and pelvic organ prolapse. Accordingly, I have included in this report my analyses of some of these products. I have also included in this report critiques of other expert reports offered in other cases in which Ethicon's mesh products have been at issue.

Ethicon's mesh product is made of Prolene mesh. Prolene is the Ethicon brand name for its mesh material. Chemically, Prolene consists of polypropylene plus the addition of five highly proprietary additives as discussed herein. Where I refer to polypropylene used in Ethicon's mesh, I am referring to the specific polypropylene and proprietary additives that make this mesh different from mesh marketed by other manufacturers. All my opinions herein are offered to a reasonable degree of scientific certainty.

I have been asked to do the following:

- Physical properties of the Prolene explant did not deteriorate but, instead, improved during implantation; and

- Prolene is stable during implantation.

Had degradation occurred, there would have been significant losses in toughness, molecular weight, and a concomitant increase in carbonyl frequency; none of which occurred during the 7 year dog study.

In summary, plaintiff experts' arguments for degradation, oxidation, and molecular weight losses after initial implantation are not supported by Burkley's data, plaintiffs' experts' data, or published literature developed from reliable scientific data.

I understand there are those who allege Prolene's structural changes *in vivo* are sufficient to affect property/device function loss. However, this tenet is not founded on factual, reliable and repeatable scientific data of which I am aware. It is my opinion, and supported by extensive and repeatable experimental data, that such proponents have historically, and erroneously, identified adsorbed protein coatings on the implant surface as polypropylene; they are mistaken. The adsorbed protein coating forms *in vivo*, and is subsequently "fixed" by the well-known chemical reaction of formaldehyde with proteins. The fixation product, with one exception, has not been removed, in the instances of which I am familiar, prior to explant testing and evaluation. Thus, these proponents have mischaracterized adsorbed protein coatings as PP and, to date, the scientific and chemical basis of their argument is non-existent.

The work of de Tayrac and Letouzey, the one exception that did not use formaldehyde as a fixation agent, further confirms this precept. De Tayrac writes that "The explanted infected mesh shows transverse cracks (a). After washing with DMSO (b) and ultrasonic shock (c), it appears marked modifications in mesh surface corresponding to the biofilm (a), and after biofilm removal, no polymer degradation was seen any more(c)." (a, b, and c are photos of explanted PP at the various stages of cleaning). Note, contrary to others who report Prolene degradation, de Tayrac did not "fix" the proteins of his sample via immersion in formalin (formaldehyde in water) solution. This is extremely significant as the fixation process produces a hard, insoluble, and brittle protein-formaldehyde polymer composite shell surrounding the fiber. It is significant that de Tayrac's decision not to use formalin fixation as part of his experimental protocol allowed him to examine the fiber without interference of the encapsulating protein-formaldehyde polymeric composite. Consequently, he was able to clean the fibers with mild reagents and conditions. In summary, when properly handled and cleaned without "fiber fixation," the fibers were devoid of a protein coating layer and essentially unchanged.

Much has been written, and literally thousands of experiments conducted, in an effort to ascertain the interrelation of synthetic mesh materials, their function, and performance in the human body. In studying these issues, I have confirmed an alarming and almost universal indifference for the underlying basic chemistry/biochemistry necessary for evaluating the efficacy of mesh materials. For instance, the typical protocol for removing mesh has been to perform explant surgery, and thereafter subject the explanted

results are unreliable. For instance, if proteins are not removed, and their presence is not known and understood, they elicit erroneous data. Consider, for example, light microscopy evaluations such as SEM and optical microscopy (LM). If all tissue and proteinaceous coatings (i.e. adsorbed protein) are not removed prior to fixation or immersion in formaldehyde, a high molecular weight, brittle, and insoluble, protein-formaldehyde polymer forms. The formaldehyde-protein polymer encapsulates or, in other terms, forms a shell of "armor" around mesh fibers. During this chemical "fixation" reaction, molecular contraction or shrinkage occurs. Subsequent drying of the mesh explant produces a hard, brittle protein-formaldehyde polymer encasing the Prolene fiber. This dry and hard protein coating will crack as it surrounds the explant and experiences movement.[70,71] Examples of this phenomenon have been observed during my SEM examinations of explanted devices similar to the example depicted in Figure 8 below. It is from a plaintiff's expert in mesh litigation.

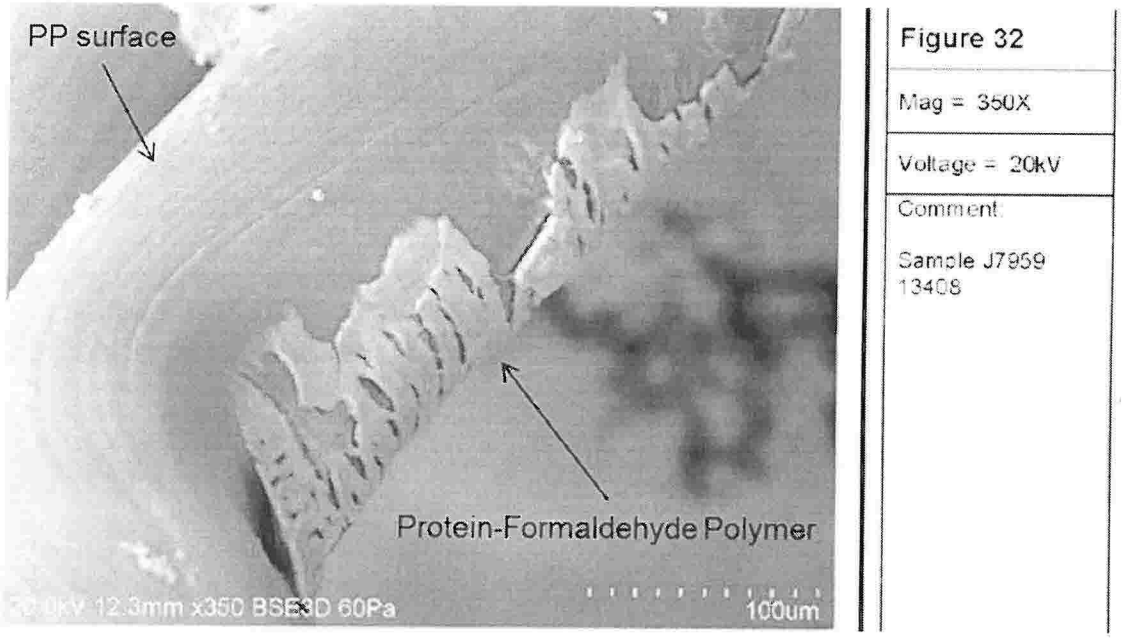


Figure 8. Example SEM micrograph taken from plaintiff's expert report in other litigation, confirming a cracked, encasing layer of protein-formaldehyde polymer.[72]

It is important to note that the surface striations or extrusion lines created during the extruding process of manufacturing Prolene fiber remain visible and unaffected after the protein coating begins to crack and fall from the fiber's surface. If surface degradation of Prolene actually occurred, the extrusion lines would no longer be present.

The chemical reaction of proteins with formaldehyde is well-known, and has been for more than 60 years. The reaction of formalin with proteins was made public in 1949 when the chemistry was first published by Heinz Fraenkel-Conrat and Dale K. Mecham.[73] It is also well established that adsorbed protein removal from a foreign body is very difficult.[74] These authors, one of whom is Dr. Robert Guidoin, wrote "In order to study the surface chemistry of explanted prostheses, it is necessary to remove all the

tissue that may have grown over and within the prosthetic structure. In the event that the explant has been treated with a fixative agent after retrieval, such as formaldehyde or glutaraldehyde, the tissue will be crosslinked and the only effective way of completely removing it is to use hydrolytic chemicals. Depending on the degree of crosslinking, strong chemicals and/or extreme hydrolysis conditions may be required."

Fraenkel-Conrat in their 1949 publication clearly described the chemical reaction transforming protein with formaldehyde into a high molecular weight, crosslinked, formaldehyde-protein polymer. The chemical reaction is shown in Figure 9.

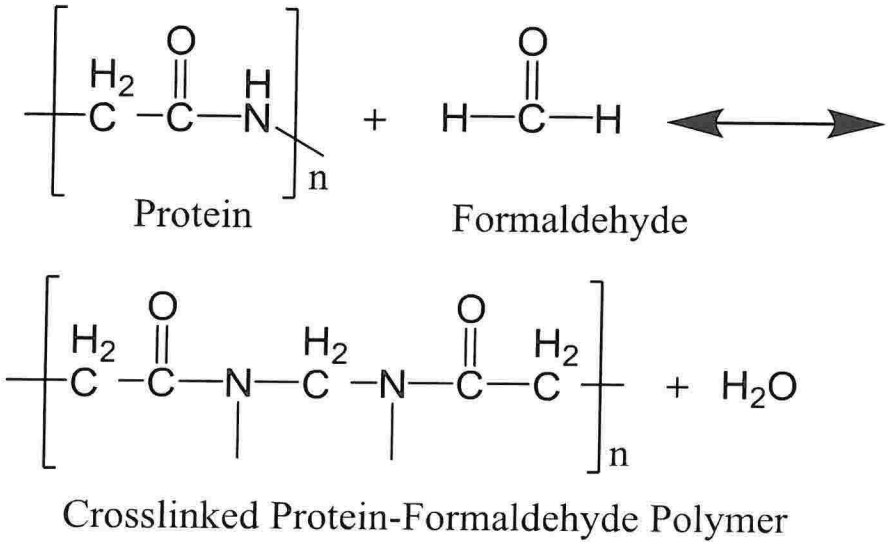


Figure 9. Reaction of protein and formaldehyde resulting in a crosslinked protein-formaldehyde polymer.

The formaldehyde-protein polymer properties are characterized by:[75,76]

- Insolubility
- Brittleness
- Hardness
- Contains at minimum, Carbon, Hydrogen, Oxygen, Nitrogen

The authors' 1949 manuscript stated "Preceding papers from this Laboratory have shown that at room temperature, and within the range of pH 3 to 9, methylene crosslinks can be formed between amino groups on the one hand and amide, guanidyl, indole, phenol, or imidazole groups on the other."[77] Numerous papers have since been written reaffirming what is a very well-known protein-formaldehyde crosslinking reaction.[78,79,80] In fact, Dr. Susan Lester has prepared a Manual of Surgical Pathology, 3rd Edition, copyrighted in 2000, 2006, and 2010 describing the fixation process.[81]

In support of Fraenkel-Conrat, *et al.*, Fox and co-workers wrote in the 1985 Journal of Histochemistry and Cytochemistry, and described formaldehyde as a tissue fixation chemical.[82] These authors brought attention to the work of Ferdinand Blum who, as early as the 1980's, was responsible for several articles on the reactions of formaldehyde as a "tissue fixation" agent. Fox, *et al.* reported when tissue is placed in formalin, "A major concern in fixation by formaldehyde, or with any fixative, is the amount of distortion produced by the fixation process. The usual term applied to fixation distortion is shrinkage."[83] These authors also note "A variety of concentrations of formaldehyde were tested for use as a fixative for electron microscopy, but no concentration of formaldehyde between 0.5 and 20% produced photomicrographs comparable with those from glutaraldehyde fixed tissues."[84]

Lester, likewise, has written that "most fixatives cause shrinkage of the tissue and offers additional information regarding formalin as a fixative."[85] Dr. Lester in the text titled "Manual of Surgical Pathology"[86] writes:

1. If exact measurements are important, they should be taken prior to fixation.

2. Unbuffered formalin degrades rapidly. Composition: 10% phosphate-buffered formalin (formalin is 40% formaldehyde) in water, does not preserve nucleic acids well.

3. Formalin is the standard fixative of most pathology departments and has been used in many studies of special stains and immunohistochemistry. It fixes most tissues well and is compatible with most histologic stains.

4. Tissue can be preserved in formalin for many months. Fixation occurs due to crosslinking of proteins.

5. Crosslinking occurs over time; therefore even small specimens (e.g., core needle biopsies) need to "fix" for a minimum of 6 to 8 hours

6. Formaldehyde, a highly reactive chemical and polar reagent, can function as an extraction solvent and/or chemically react with other non-protein chemicals, i.e. "Lipids and carbohydrates are often lost during processing unless special techniques are used."

In the review *Crosslinking fixatives: what they are, what they do, and why we use them,* the authors discuss formaldehyde and its preference for reacting with proteins during the fixation process.[87] These concepts are illustrated in Figure 10.

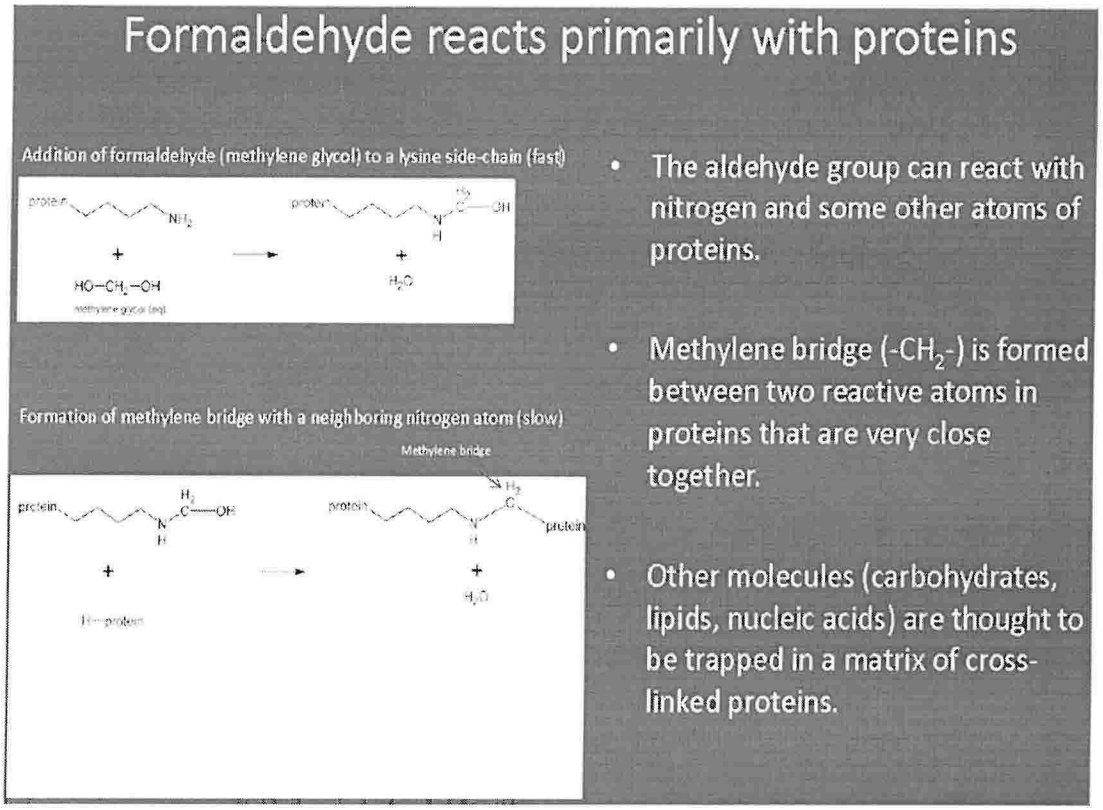
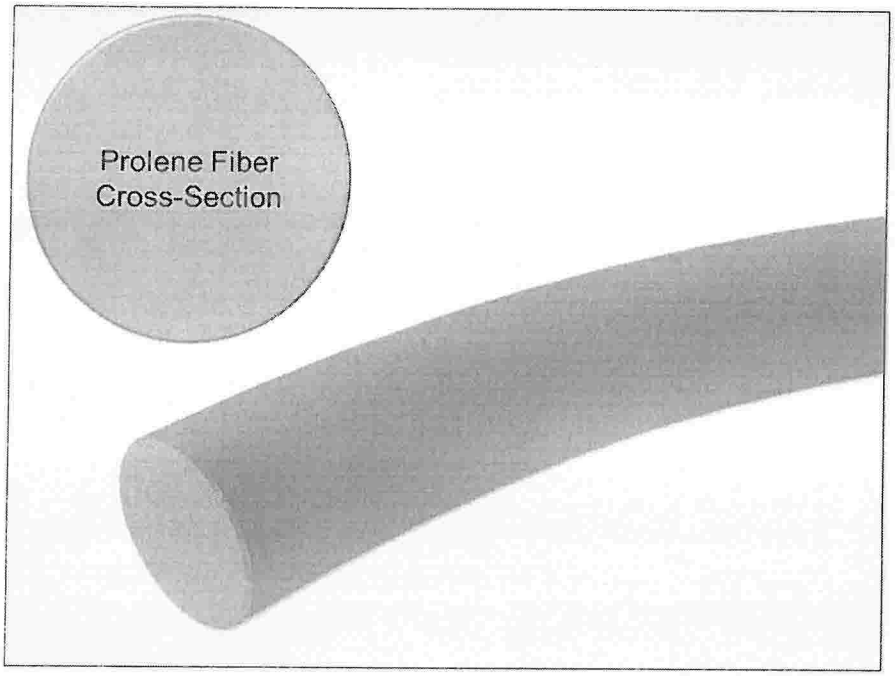


Figure 10. Formaldehyde reactions with proteins during the fixation process.[88]

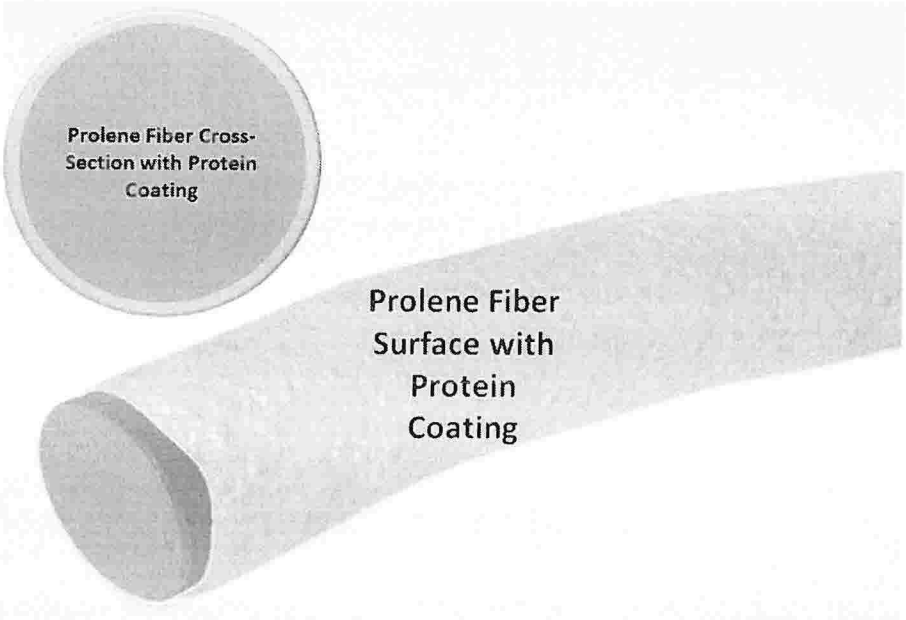
In summary, the well-known reaction of proteins and formaldehyde produces a hard, brittle, insoluble crosslinked polymer that defines the basis of flesh "fixation" long known and used by histologists and pathologists. However, as noted, the formaldehyde-protein polymer is extremely difficult to remove from mesh fibers. Therefore, interpretation of much of the printed analytical data derived from formalin-treated explants is suspect and, frankly, unreliable unless special consideration is given to the presence and chemical reactivity as well as an appropriate cleaning protocol.

Figure 11 illustrates the protein-formaldehyde encapsulation of Prolene fibers and subsequent cracking of the protein-formaldehyde shell surrounding the fibers.

a) A pristine Prolene fiber used in Ethicon's mesh.



b) After the pristine, Prolene mesh is implanted, within milliseconds protein coatings immediately form around and through the mesh.[89]



c) The Explanted Mesh with protein coating attached is placed in a formalin (formaldehyde) solution. The Formaldehyde-Protein Fixation Chemical

Reaction begins and continues for as long as the mesh is in formalin. The formed and crosslinked adsorbed protein coating is brittle, insoluble and hard. The brittle and hard casing around the Prolene fiber will crack with drying and/or physical manipulation.

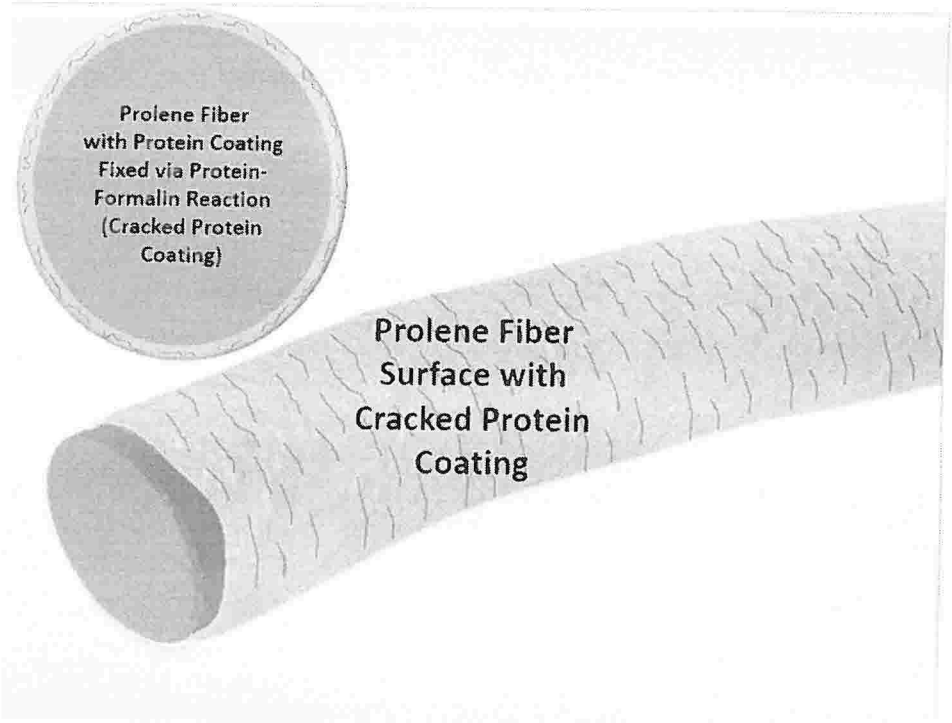


Figure 11. Protein-formaldehyde encapsulation of Prolene fibers and subsequent cracking of the crosslinked protein-formaldehyde shell.

The writings of others, as noted by Iakovlev[90], including but not limited to the work of Costello *et al.*[91], have claimed, without definitive scientific evidence, that explanted PP degraded to the extent its intended use has been compromised. For instance, Costello boldly concluded that "…explanted PP meshes did undergo degradation while *in vivo*…" Clavé further clouds the issue of PP stability with his manuscript titled "*Polypropylene as a reinforcement in pelvic surgery is not inert: comparative analysis of 100 explants*".[92] Costello's statements are misleading in that he had no analytical data supportive of his conclusion, which was "The studies provide evidence contrary to published literature characterizing PP as inert in such applications." Furthermore, Clavé purports to perform DSC to identify *in vivo* changes or "degradation" of PP via changes in glass transition temperature (T_g), melting temperature, and heat of fusion. However, he goes on to report DSC thermograms of what he referred to as treated, degraded, and non-degraded LDPPMF (low density polypropylene multi-filament) explants were all similar to treated pristine Prolene. Additionally, his experimental evidence via DSC thermograms of so-called "degraded" and non-degraded HDPPMF (high density polypropylene multi-filament) explants were reported as being similar to those of the treated, pristine, Prolene samples.[93] It is inconsistent with scientific principles for Clavé to suggest that degraded, non-degraded, and pristine Prolene all possess similar DSC thermograms.

I reserve the right to supplement this initial report and analysis, create additional exhibits as necessary to illustrate my testimony based upon the receipt of additional information, documents and materials, and to revise this report following the receipt of additional information and/or materials that have not yet been made available. As a supplement to my general report I rely on case specific reports served herewith.

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[1] Permeability Properties of Plastics and Elastomers, A Guide to Packaging and Barrier Materials, Chapter 45, Plastics Design Library, 13 Easton Avenue, Norwich, NY 13815; Copyright 2003, Second Edition, by Liesl K. Massey
[2] Material Safety Data Sheet, ETH.MESH.00918015
[3] Polypropylene for Medical Applications, Portnoy, R. C., Business Briefing: Medical Device Manufacturing and Technology, 2002.
[4] Engineering Materials Handbook, Vol. 2, Engineering Plastics, ASM International, Metal Park, OH 44073; copyright 1988, pages 64-65 and pages 32, 58, 65,192-193 and 446
[5] MATWEB, Material Property Data, Overview of Materials for Polypropylene, Extrusion Grade
[6] Practical Guide to Polypropylene, Tripathi, David, ISBN-13:9781859572825, Rapra Technology Ltd., April 28, 2002
[7] Engineering Materials Handbook, Vol. 2, Engineering Plastics, ASM International, Metal Park, OH 44073; copyright 1988, pages 64-65 and pages 32, 58, 65,192-193 and 446
[8] March, J., Advanced Organic Chemistry; Reactions, Mechanisms, and Structure; John Wiley and Sons, Third Ed., 1985, p.14
[9] Engineered Material Handbook, VOl.2, Engineering Plastics, ASM International, 1988;
[10] Permeability Properties of Plastics and Elastomers, A Guide to Packaging and Barrier Materials, Chapter 45, Plastics Design Library, 13 Easton Avenue, Norwich, NY 13815; Copyright 2003, Second Edition, by Liesl K. Massey
[11] Pharmacodynamics, Acid-Base Properties of Drugs, page 1-6
[12] Al-Malaika, S., "Photostabilizers." Polypropylene – An A-Z Reference, Ed. J. Karger-Kocsis. London: 1999, 581-590
[13] Al-Malaika, S., "Photostabilizers." Polypropylene – An A-Z Reference, Ed. J. Karger-Kocsis. London: 1999, 581-590
[14] Pharmacodynamics, Acid-Base Properties of Drugs, page 1-6
[15] Permeability Properties of Plastics and Elastomers, A Guide to Packaging and Barrier Materials, Chapter 45, Plastics Design Library, 13 Easton Avenue, Norwich, NY 13815; Copyright 2003, Second Edition, by Liesl K. Massey
[16] Williams, D.F., J. Material Science, 17, 1982 (1233-1246); Williams, D.F. Clinical Materials, Vol. 10 (1992) 9-12
[17] Williams, D.F., J. Material Science, 17, 1982 (1233-1246); Williams, D.F. Clinical Materials, Vol. 10 (1992) 9-12
[18] Burkley, D.F., Seven Year Data for Ten Year Prolene Study, October 15, 199, ETH.MESH.05453719-05453727
[19] Engineered Material Handbook, VOl.2, Engineering Plastics, ASM International, 1988;
[20] Engineered Material Handbook, VOl.2, Engineering Plastics, ASM International, 1988;
[21] Carew, Evelyn, O., Cooke, Francis, W., Lemons, Jack, E., Ratner, Buddy, D., Vesely, Ivan, Vogler, Erwin, "Properties of Materials." Biomaterials Science, An Introduction to Materials in Medicine, Ed. Buddy D. Ratner, Allan S. Hoffman, Frederick J. Schoen, Jack E. Lemon, London: 2004, 23-65
[22] Murariu, M., Da Silva Ferreira, A., Pluta, M., Bonnaud, L., Alexandre, M., and Dubios, P., "Polylactide (PLA)–CaSO4 composites toughened with low molecular weight and polymeric ester-like plasticizers and related performances", European Polymer Journal, 44 (2008), 3842-3852
[23] N. S. Vinidiktova, Zh. V. Kadolich, Deformation Strength Properties of Polypropylene Modified with Various Plasticizers, Tekhnologii, Instrumenty (2006), 11(3), 66-71
[24] Ermilova G.A., Ragozina I.A., Leontjeva N.M., Effect of High-molecular-weight Plasticizers on the Properties of Polypropylene, UDC 678.742.3.19:678.742.01:53